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Article

Nomograms for Differentiated Thyroid Carcinoma Patients Based on the Eighth AJCC Staging and Competing Risks Model

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Abstract

Background: Differentiated thyroid carcinoma (DTC) patients have a long survival period and good prognosis, so they are easily affected by competing risk events. The purpose of this study was to use the competing risks model to identify prognostic factors for cause-specific death (CSD) and death due to other causes (DOC) in patients with DTC. **Methods:** Our screening process identified 34 585 DTC patients in the Surveillance, Epidemiology, and End Results database and randomly divided them into a training cohort and a validation cohort. We used the Fine and Gray subdistribution hazards model to establish the CSD and DOC nomograms. The distinguishing ability and consistency of the nomograms were evaluated using the consistency indexes and calibration plots. **Results:** Our analysis of a competing risks model revealed that pathological grade, tumor size, histological type, American Joint Committee on Cancer (AJCC)–8 stage, surgery status, adjuvant radiotherapy status, adjuvant chemotherapy status, and log odds of positive lymph nodes are prognostic factors for CSD, and age at diagnosis, year of diagnosis, sex, pathological grade, tumor size, AJCC-8 stage, surgery status, adjuvant radiotherapy status, and lymph node ratio are prognostic factors for DOC. The 1-year, 3-year, and 5-year concordance indexes in the validation cohorts were 0.942, 0.931, and 0.913 for the CSD nomogram and 0.813, 0.746, and 0.776 for the DOC nomogram. The calibration plots showed good consistency in both nomograms. **Conclusions:** Our nomograms can be used as a tool to help clinicians individually predict the probability of CSD and DOC in DTC patients at 1 year, 3 years, and 5 years, which has certain guiding value in clinical applications.

The main types of thyroid cancer are papillary carcinoma, follicular carcinoma, medullary carcinoma, and undifferentiated carcinoma. Papillary carcinoma and follicular carcinoma are collectively called differentiated thyroid carcinoma (DTC), which accounts for more than 95% of all thyroid cancers (1). Thyroid cancer is becoming more common (2), and it is predicted to replace colorectal cancer as the fourth most prevalent cancer by 2030 (3). Although the increasing incidence of thyroid cancer is at least partly due to increased diagnosis rates, its increasing prevalence indicates the need to pay more attention to the prognosis of thyroid cancer and individualized treatments (4,5).

Competing risk events refer to competing outcomes that may occur in addition to the disease outcome of interest (6). Competing risk models are becoming more well-known and used in various cancers, including renal cell carcinoma and rectal cancer (7,8). For cancer with a longer course of the disease, competing risk events have greater interference with cancer-specific death. DTC patients have a long survival period and good prognosis, so they are easily affected by competing risk events. However, the existing research on the competing risks of DTC appears to be insufficient. The purpose of this study was to use a competing risks model to analyze the prognostic factors for cause-specific death (CSD) and death due to other causes (DOC) in DTC patients based on the American Joint Committee on Cancer (AJCC)–8 stage.

A nomogram is a simple and easy-to-use predictive tool in which points are assigned to each factor according to its degree of influence on the outcome of interest. The scores are added to obtain the total score, which is used to calculate the

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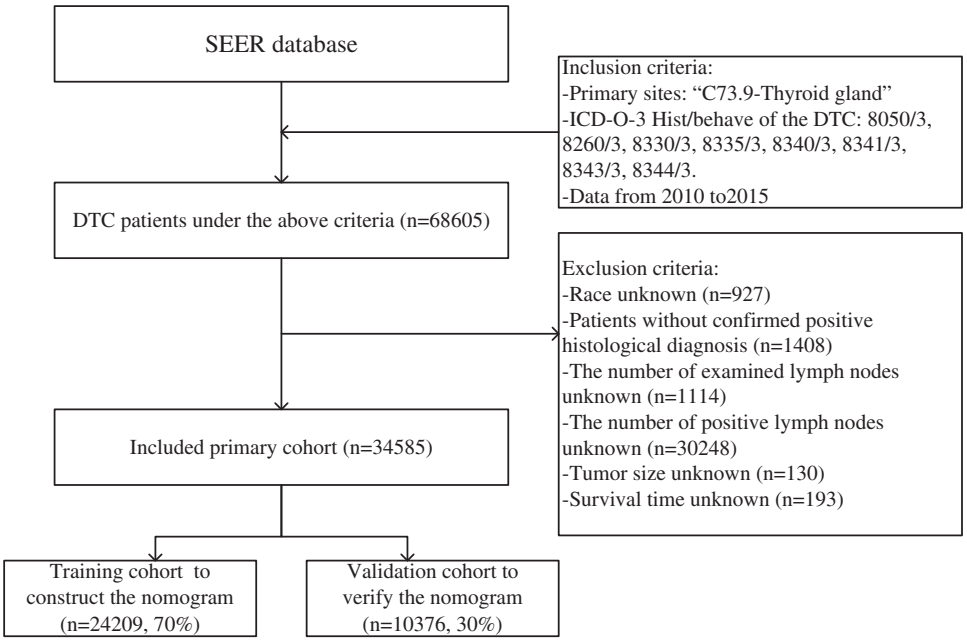

Figure 1. Data screening and sorting flowchart. DTC = differentiated thyroid carcinoma; ICD-O-3 = the third revision of the *International Classification of Diseases for Oncology*; SEER = Surveillance, Epidemiology, and End Results.

Table 1. Basic characteristics of the DTC patients

Variable	Training cohort	Validation cohort	P[a]
No. of patients, No. (%)	24 209 (70.0)	10 376 (30.0)	
Age, No. (%)			.49
<55 y	16 156 (66.7)	6885 (66.4)	
≥55 y	8053 (33.3)	3491 (33.6)	
Year of diagnosis, No. (%)			.47
2010-2012	11 303 (46.7)	4888 (47.1)	
2013-2015	12 906 (53.3)	5488 (52.9)	
Race, No. (%)			.24
White	20 429 (84.4)	8684 (83.7)	
Black	961 (4.0)	440 (4.2)	
Other	2819 (11.6)	1252 (12.1)	
Sex, No. (%)			<.001
Male	5525 (22.8)	2549 (24.6)	
Female	18 684 (77.2)	7827 (75.4)	
Marital status, No. (%)			.30
Married	17 273 (71.3)	7451 (71.8)	
Single	5517 (22.8)	2360 (22.7)	
Other	1419 (5.9)	565 (5.4)	
Grade, No. (%)			.86
I	5257 (21.7)	2249 (21.7)	
II	1027 (4.2)	432 (4.2)	
III	211 (0.9)	79 (0.8)	
IV	63 (0.3)	25 (0.2)	
Other	17 651 (72.9)	7591 (73.2)	
Laterality, No. (%)			.15
Left	599 (2.5)	251 (2.4)	
Right	819 (3.4)	322 (3.1)	
Bilateral	225 (0.9)	76 (0.7)	
Other	22 566 (93.2)	9727 (93.7)	
Size, No. (%)			.50
<2 cm	15 151 (62.6)	6434 (62.0)	
2-3.9 cm	6421 (26.5)	2815 (27.1)	
≥4 cm	2637 (10.9)	1127 (10.9)	

(continued)

Table 1. (continued)

Variable	Training cohort	Validation cohort	P[a]
Histological type, No. (%)			.99
8260/3: Papillary adenocarcinoma, NOS	15 025 (62.1)	6460 (62.3)	
8340/3: Papillary carcinoma, follicular variant	6748 (27.9)	2871 (27.7)	
8341/3: Papillary microcarcinoma	753 (3.1)	329 (3.2)	
8050/3: Papillary carcinoma, NOS	507 (2.1)	215 (2.1)	
8344/3: Papillary carcinoma, columnar cell	416 (1.7)	182 (1.8)	
8343/3: Papillary carcinoma, encapsulated	122 (0.5)	54 (0.5)	
8330/3: Follicular adenocarcinoma, NOS	480 (2.0)	193 (1.9)	
8335/3: Follicular carcinoma, minimally invasive	158 (0.7)	72 (0.7)	
AJCC-8 stage, No. (%)			.27
I	20 176 (83.3)	8606 (82.9)	
II	3423 (14.1)	1500 (14.5)	
III	308 (1.3)	116 (1.1)	
IVA	115 (0.5)	60 (0.6)	
IVB	187 (0.8)	94 (0.9)	
Surgery, No. (%)			.14
Yes	24 158 (99.8)	10 362 (99.9)	
No/Unknown	51 (0.2)	14 (0.1)	
Adjuvant radiotherapy, No. (%)			.33
Yes	13 331 (55.1)	5654 (54.5)	
No/Unknown	10 878 (44.9)	4722 (45.5)	
Adjuvant chemotherapy, No. (%)			.39
Yes	79 (0.3)	40 (0.4)	
No/Unknown	24 130 (99.7)	10 336 (99.6)	
ELN, No. (%)			.60
I	14 897 (61.5)	6328 (61.0)	
II	6216 (25.7)	2713 (26.1)	
III	3096 (12.8)	1335 (12.9)	
PLN, No. (%)			.92
I	14 167 (58.5)	6047 (58.3)	
II	5413 (22.4)	2331 (22.5)	
III	4629 (19.1)	1998 (19.3)	
LNR, No. (%)			.49
I	14 185 (58.6)	6059 (58.4)	
II	4885 (20.2)	2059 (19.8)	
III	5139 (21.2)	2258 (21.8)	
LODDS, No. (%)			.15
I	10 261 (42.4)	4465 (43.0)	
II	6509 (26.9)	2685 (25.9)	
III	7439 (30.7)	3226 (31.1)	

[a]The P values were calculated by χ^2 tests and were 2-sided. AJCC = American Joint Committee on Cancer; DTC = differentiated thyroid carcinoma; ELN = examined lymph nodes; LNR = lymph nodes ratio; LODDS = log odds of positive lymph nodes; NOS = not otherwise specified; PLN = positive lymph nodes.

predicted probability of the individual outcome event (9). At present, research has developed some prognostic nomograms of thyroid cancer. The research of Wen et al. (10) and Tong et al. (11) did not consider the existence of competitive risk. Yang et al. (12) and Wang et al. (13) used competitive risk models to construct prognostic models for patients with thyroid cancer and papillary thyroid microcarcinoma, respectively. However, because of the limitation of research time or other reasons, all current nomograms constructed using the Surveillance, Epidemiology, and End Results (SEER) database have not used the AJCC-8 stage for analysis, which makes further research very necessary.

Lymph node metastasis has always been an important prognostic factor for thyroid cancer. In addition to the number of examined lymph nodes (ELN) and the number of positive lymph nodes (PLN), recent studies have proposed some improved lymph node indicators, including lymph node ratio (LNR) and the log odds of positive lymph nodes (LODDS) (14,15). These indicators have not been uniformly and clearly studied in DTC patients. Therefore, we believe that a comprehensive analysis is necessary to determine the best prognostic lymph node indicators for DTC patients. LNR defined as the quotient of the number of positive lymph nodes was used to quantify the lymph nodes (16), and LODDS was defined as the logarithm of the ratio between the numbers of positive and negative lymph nodes (17). In addition to general lymph node prognostic factors, some studies in recent years have found that LNR and LODDS may be prognostic factors for certain cancers, including those of the breast, stomach, and colon (18-20). However, this has not been confirmed in DTC patients, and so we hypothesized that LNR and LODDS are important predictors of outcomes in DTC. In this study, we also planned to establish corresponding prognostic nomograms for assessing the likelihoods of CSD and DOC outcomes.

Table 2. Cumulative incidences of cause-specific death and death due to other causes

Variables	Cause-specific death					Death due to other causes				
	1-year	3-year	5-year	Gray test	P[a]	1-year	3-year	5-year	Gray test	P[a]
Age, y				164.280	<.001				472.120	<.001
<55	0.001	0.001	0.003			0.002	0.006	0.012		
≥55	0.007	0.015	0.023			0.013	0.043	0.075		
Year of diagnosis				2.651	.10				13.455	<.001
2010-2012	0.002	0.005	0.009			0.005	0.016	0.030		
2013-2015	0.003	0.007	NA			0.006	0.023	NA		
Race				0.288	.87				5.155	.08
White	0.003	0.006	0.009			0.006	0.019	0.033		
Black	0.001	0.005	0.015			0.003	0.026	0.056		
Other	0.003	0.005	0.010			0.007	0.015	0.028		
Sex				29.075	<.001				158.896	<.001
Male	0.006	0.011	0.017			0.012	0.039	0.064		
Female	0.002	0.005	0.008			0.004	0.013	0.024		
Marital status				4.631	.10				13.138	.001
Married	0.003	0.007	0.011			0.006	0.020	0.037		
Single	0.002	0.005	0.008			0.005	0.014	0.023		
Other	0.001	0.003	0.007			0.005	0.015	0.029		
Grade				1336.397	<.001				132.030	<.001
I	0.001	0.003	0.006			0.005	0.019	0.034		
II	0.001	0.005	0.014			0.003	0.024	0.043		
III	0.043	0.106	0.140			0.029	0.060	0.137		
IV	0.291	0.346	0.378			0.131	0.208	0.246		
Other	0.002	0.004	0.008			0.005	0.017	0.030		
Laterality				3.816	.28				0.191	.98
Left	0.003	0.007	0.007			0.009	0.017	0.034		
Right	0.002	0.007	0.018			0.006	0.016	0.033		
Bilateral	0.000	0.000	0.000			0.000	0.007	0.055		
Other	0.003	0.006	0.010			0.006	0.019	0.033		
Size, cm				200.587	<.001				48.261	<.001
<2	0.001	0.003	0.004			0.005	0.017	0.029		
2-3.9	0.002	0.007	0.012			0.005	0.018	0.032		
≥4	0.014	0.025	0.037			0.012	0.033	0.059		
Histological type				68.310	<.001				21.261	<.001
8260/3: Papillary adenocarcinoma, NOS	0.003	0.007	0.010			0.005	0.019	0.032		
8340/3: Papillary carcinoma, follicular variant	0.002	0.003	0.006			0.005	0.019	0.036		
8341/3: Papillary microcarcinoma	0.000	0.000	0.000			0.008	0.010	0.017		
8050/3: Papillary carcinoma, NOS	0.004	0.004	0.007			0.008	0.015	0.015		
8344/3: Papillary carcinoma, columnar cell	0.012	0.032	0.046			0.012	0.040	0.068		
8343/3: Papillary carcinoma, encapsulated	0.008	0.008	0.008			0.017	0.040	0.055		
8330/3: Follicular adenocarcinoma, NOS	0.006	0.014	0.031			0.004	0.017	0.047		
8335/3: Follicular carcinoma, minimally invasive	0.000	0.014	0.014			0.007	0.017	0.017		
AJCC-8 stage				2043.179	<.001				477.752	<.001
I	0.000	0.001	0.002			0.003	0.012	0.022		
II	0.006	0.011	0.021			0.013	0.045	0.079		
III	0.039	0.089	0.106			0.036	0.076	0.109		
IVA	0.080	0.218	0.271			0.062	0.141	0.246		
IVB	0.102	0.178	0.259			0.049	0.129	0.162		
Surgery				40.994	<.001				72.673	<.001
Yes	0.003	0.006	0.010			0.006	0.018	0.033		
No/Unknown	0.059	0.091	0.091			0.080	0.175	0.221		
Adjuvant radiotherapy				4.106	<.001				17.363	<.001
Yes	0.003	0.007	0.011			0.004	0.015	0.029		
No/Unknown	0.003	0.005	0.008			0.008	0.023	0.038		
Adjuvant chemotherapy				664.168	<.001				23.590	<.001

(continued)

Table 2. (continued)

Variables	Cause-specific death					Death due to other causes				
	1-year	3-year	5-year	Gray test	P[a]	1-year	3-year	5-year	Gray test	P[a]
Yes	0.180	0.243	0.284			0.080	0.096	0.140		
No/Unknown	0.002	0.005	0.009			0.005	0.018	0.033		
ELN				65.133	<.001				30.535	<.001
I	0.002	0.003	0.007			0.005	0.017	0.032		
II	0.003	0.006	0.012			0.004	0.015	0.028		
III	0.008	0.018	0.021			0.012	0.032	0.050		
PLN				122.931	<.001				21.530	<.001
I	0.000	0.001	0.004			0.005	0.015	0.030		
II	0.005	0.009	0.013			0.007	0.027	0.042		
III	0.007	0.016	0.024			0.007	0.020	0.031		
LNR				103.240	<.001				15.258	<.001
I	0.001	0.001	0.004			0.005	0.015	0.031		
II	0.006	0.013	0.019			0.008	0.026	0.039		
III	0.006	0.012	0.017			0.007	0.021	0.034		
LODDS				87.887	<.001				1.397	.50
I	0.001	0.002	0.003			0.006	0.017	0.035		
II	0.002	0.004	0.010			0.005	0.018	0.030		
III	0.006	0.013	0.019			0.006	0.021	0.034		

[a]The *P* values were calculated by Gray tests and were 2-sided. AJCC = American Joint Committee on Cancer; ELN = examined lymph nodes; LNR = lymph nodes ratio; LODDS = log odds of positive lymph nodes; NOS = not otherwise specified; PLN = positive lymph nodes.

Methods

Data Selection

The research data were obtained from the SEER program (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 18 Regs Custom Data (with additional treatment fields) based on the November 2018 submission, which covers approximately 27.8% of the US population. The chemotherapy data require an additional application, and all data were downloaded using SEER*Stat software (version 8.3.8) (21). Because some of the SEER research data are publicly available, informed consent and institutional review board approval were not required. We extracted DTC patients from the SEER database using the third revision of the *International Classification of Diseases for Oncology* (ICD-O-3) code C73.9-thyroid gland to select the primary sites of DTC and representative ICD-O-3 histology and behavior codes related to DTC (8050/3, 8260/3, 8330/3, 8335/3, 8340/3, 8341/3, 8343/3, and 8344/3). Each ICD-O-3 code included more than 100 patients.

Age at diagnosis, year of diagnosis, race, sex, and marital status were selected as demographic characteristics. The following pathological variables were also included: grade, laterality, tumor size, AJCC-8 stage, surgery status, radiotherapy status, chemotherapy status, ELN, PLN, LNR, and LODDS. Because the AJCC-7 stage system in the SEER database was only recorded in 2010-2015, we actually selected the patients diagnosed at 2010-2015 for analysis.

Data Processing

Based on AJCC-8 stage and the recommendations of multi-institutional research (22,23), we divided the age at diagnosis into 2 categories using 55 years as the cutoff. The tumor size was divided into 3 categories according to the diameter: less than 2 cm, 2-3.9 cm, and 4 or more cm. Because the SEER database does not directly include data from AJCC-8 stage, we integrated that system for DTC according to the equivalents of the seventh edition of the TNM classification (22). We used the age in the SEER database and the seventh edition of the TNM staging system to rationally reclassify all patients so that they conformed with the increase in the age cutoff in AJCC-8 stage. LNR was calculated as the number of positive regional nodes divided by the total number of regional nodes examined. LODDS was estimated as log(pnod + 0.5)/(tnod—pnod + 0.5), where pnod is the number of positive nodes and tnod is the number of examined nodes, and 0.5 is added to both the numerator and denominator to avoid infinite numbers (19).

The exclusion criteria for the data were no confirmed positive histological diagnosis or unknown race, number of examined lymph nodes, number of positive lymph nodes, tumor size, or survival time. We eventually retained 34 585 patients for further analysis. The detailed data screening and sorting steps are shown in Figure 1.

The study outcomes included survival, CSD, and DOC. Patients were followed up until their death or loss of follow-up or until the end of 2016. The survival time was reported in months.

Statistical Analysis

The 34 585 selected DTC patients were randomly divided into a training cohort (70%, n = 24 209) and a validation cohort (30%, n = 10 376) using R software (version 3.5.3, R Foundation for Statistical Computing, Vienna, Austria). We first used SPSS (version 23.0, IBM Corporation, Armonk, NY) to describe the baseline information of the 2 cohorts and conducted χ^2 tests to confirm homogeneity between the 2 cohorts of data. Because there is no standard for the classification of ELN, PLN, LNR, and LODDS and the clinical significance of analyzing them as continuous variables is difficult to interpret, we used X-tile (Yale University School of Medicine, New Haven, CT) to determine the best cutoff points for them. We use the patient's survival time and specific death outcome to divide different lymph node

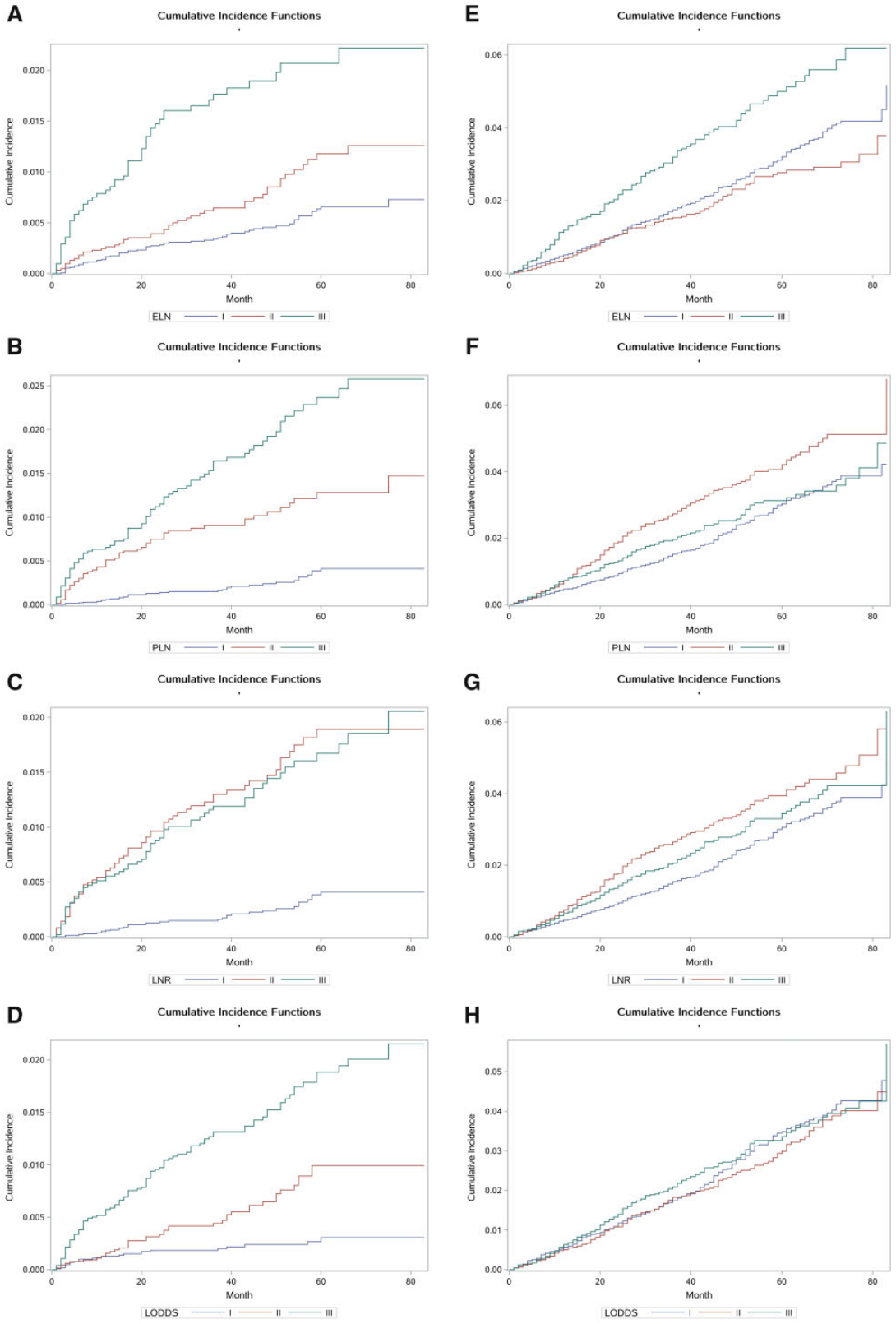

Figure 2. The cumulative incidence function curves for lymph node variables. Curves for cause-specific death for **(A)** ELN, **(B)** PLN, **(C)** LNR, and **(D)** LODDS and death due to other causes for **(E)** ELN, **(F)** PLN, **(G)** LNR, and **(H)** LODDS are shown. ELN = examined lymph nodes; LNR = lymph node ratio; LODDS = log odds of positive lymph nodes; PLN = positive lymph nodes.

Table 3. Multivariate cause-specific death and death due to other causes analysis for prognostic performance of different lymph node variables[a]

Lymph node variables	C-index			Goodness of fit	
	1-year	3-year	5-year	AIC	BIC
Cause-specific death					
Examined lymph nodes	0.955	0.934	0.899	2622.67	2812.44
Positive lymph nodes	0.954	0.944	0.903	2595.45	2785.21
Lymph nodes ratio	0.955	0.943	0.902	2607.91	2797.67
LODDS	0.958	0.942	0.907	2589.55	2779.31
Death due to other causes					
Examined lymph nodes	0.797	0.791	0.771	55 818.46	55 887.15
Positive lymph nodes	0.796	0.792	0.770	55 703.26	55 771.95
Lymph nodes ratio	0.798	0.795	0.772	55 657.21	55 725.90
LODDS	0.797	0.790	0.772	55 754.67	55 823.36

[a]AIC = Akaike information criterion; BIC = Bayes information criterion; C-index = consistency index; LODDS = log odds of positive lymph nodes.

indicators into 3 levels with minimum *P* values for the log-rank test (24).

For the CSD model, competing risk events refer to other causes of death, such as death from diseases other than DTC or accidental death. For the DOC model, the competing risk event refers to the specific death of DTC. We next used the cumulative incidence function (CIF) to predict the 1-year, 3-year, and 5-year mortality rates for CSD and DOC in univariate analyses, with Gray test used to detect intergroup differences. Finally, based on the results of the univariate analyses, the subdistribution hazard function was used to construct a multivariate competing risks model (25).

Because the lymph node indicators reflect the same information to a certain extent, ELN, PLN, LNR, and LODDS are included in 4 different multivariate competitive risk models to avoid multicollinearity. We used the consistency index (C-index), Akaike information criterion (AIC), and Bayes information criterion (BIC) to judge the discrimination and goodness of fit of the model. Both AIC and BIC are indicators to evaluate the effect of model fitting. We select the model with the lowest AIC and BIC scores for subsequent analysis (26). The final results obtained from the model were used to identify the statistically significant prognostic factors of DTC, and R software was used to construct the 1-year, 3-year, and 5-year CSD and DOC prognosis nomograms for DTC patients. The distinguishing ability and consistency of the established nomograms were evaluated using the C-indexes and calibration plots.

All statistical tests were conducted using SPSS, R software, and SAS (version 9.4, SAS Institute, Cary, NC). Probability values of a *P* value no more than .05 were considered to be indicative of statistical significance in 2-sided tests.

Results

Basic Information

Table 1 presents the baseline information of the training and validation cohorts. In terms of demographics, the majority of patients were aged younger than 55 years (66.7% and 66.4% in the training and validation cohorts), White (84.4% and 83.7%), female (77.2% and 75.4%), and married (71.3% and 71.8%), respectively. In terms of clinicopathological characteristics, the degree of malignancy of the DTC patients was relatively low, with about 62.6% and 62.0% of patients having a tumor size of less than 2 cm and about 83.3% and 82.9% being in AJCC-8 stage I. In terms of treatment, the vast majority of patients had received surgery but not adjuvant chemotherapy.

The best cutoff points calculated by X-tile divide ELN into the following 3 categories: ELN I (1–5), ELN II (6–18), and ELN III (19–89). Similarly, PLN was classified as PLN I (0), PLN II (1–3), and PLN III (4–55). LNR was classified as LNR I (0-0.022), LNR II (0.023-0.433), and LNR III (0.434-1). LODDS was classified as LODDS I (-2.253 to -0.690), LODDS II (-0.689 to -0.455), and LODDS III (-0.454 to 1.756) (Supplementary Figure 1, available online).

Cumulative Incidence Function

We used univariate analyses to analyze the study variables individually and calculated the 1-year, 3-year, and 5-year cumulative incidence rates of CSD and DOC in the training cohort. Table 2 showed that the age at diagnosis, sex, pathological grade, tumor size, histological type, AJCC-8 stage, surgery status, adjuvant radiotherapy status, adjuvant chemotherapy status, ELN, PLN, LNR, and LODDS were all statistically significantly related to CSD ($P < .05$). Meanwhile, the age at diagnosis, year of diagnosis, sex, marital status, pathological grade, tumor size, histological type, AJCC-8 stage, surgery status, adjuvant radiotherapy status, adjuvant chemotherapy status, ELN, PLN, and LNR were all related to DOC ($P < .05$).

The 1-year, 3-year, and 5-year cumulative incidences and *P* values are presented in Table 2. The CIF diagrams of lymph node variables are shown in Figure 2, and the remaining CIF diagrams are shown in the Supplementary Figure 2 (available online).

Subdistribution Hazard Function

We conducted multivariate competing risks analyses of the meaningful variables ($P < .05$) obtained in the univariate analyses. As shown in Table 3, among the 4 different CSD models, LODDS show better prognostic performance (1-year C-index = 0.958; 3-year C-index = 0.942; 5-year C-index = 0.907; AIC = 2589.55; BIC = 2779.31) than other indicators. Among the 4 different DOC models shown in Table 3, LNR shows better prognostic performance (1-year C-index = 0.798; 3-year C-index = 0.795; 5-year C-index = 0.772; AIC = 55 657.21; BIC = 55 725.90) than other indicators.

As shown in Table 4, the competing risks model for CSD revealed that the following prognostic risk factors were statistically significant: pathological grade III (vs grade I: hazard ratio

Table 4. Multivariate competing risks model analysis for cause-specific death and death due to other causes

Variables	Cause-specific death		Death due to other causes	
	HR (95% CI)	P[a]	HR (95% CI)	P[a]
Age, y		.17		<.001
<55	Referent		Referent	
≥55	0.47 (0.16 to 1.37)	.17	5.24 (3.99 to 6.87)	<.001
Year of diagnosis				.01
2010-2012	—		Referent	
2013-2015	—		1.27 (1.05 to 1.54)	.01
Race				
White	—		—	
Black	—		—	
Other	—		—	
Sex		.78		<.001
Male	Referent		Referent	
Female	0.95 (0.68 to 1.34)	.78	0.50 (0.42 to 0.60)	<.001
Marital status				.43
Married	—		Referent	
Single	—		1.12 (0.89 to 1.42)	.33
Other	—		0.87 (0.60 to 1.26)	.45
Grade		<.001		.01
I	Referent		Referent	
II	0.92 (0.40 to 2.09)	.84	1.17 (0.80 to 1.72)	.42
III	4.36 (2.12 to 8.96)	<.001	1.83 (1.08 to 3.12)	.03
IV	5.87 (2.67 to 12.88)	<.001	2.19 (1.05 to 4.56)	.04
Other	1.20 (0.75 to 1.94)	.45	0.90 (0.73 to 1.10)	.30
Laterality				
Left	—		—	
Right	—		—	
Bilateral	—		—	
Other	—		—	
Size, cm		.02		.008
<2	Referent		Referent	
2-3.9	1.19 (0.76 to 1.86)	.44	1.15 (0.93 to 1.41)	.19
≥4	1.89 (1.18 to 3.03)	.008	1.50 (1.16 to 1.93)	.002
Histological type		<.001		.29
8260/3: Papillary adenocarcinoma, NOS	Referent		Referent	
8340/3: Papillary carcinoma, follicular variant	0.70 (0.45 to 1.08)	.11	1.03 (0.85 to 1.25)	.76
8341/3: Papillary microcarcinoma	0.00 (0.00 to 0.00)	<.001	0.54 (0.29 to 1.03)	.06
8050/3: Papillary carcinoma, NOS	0.68 (0.21 to 2.24)	.53	0.64 (0.33 to 1.26)	.20
8344/3: Papillary carcinoma, columnar cell	1.74 (0.91 to 3.36)	.10	1.27 (0.78 to 2.04)	.34
8343/3: Papillary carcinoma, encapsulated	1.91 (0.35 to 10.56)	.46	1.80 (0.74 to 4.41)	.20
8330/3: Follicular adenocarcinoma, NOS	1.07 (0.48 to 2.38)	.87	0.89 (0.52 to 1.53)	.67
8335/3: Follicular carcinoma, minimally invasive	3.70 (0.94 to 14.57)	.06	0.74 (0.23 to 2.35)	.61
AJCC-8 stage		<.001		.01
I	Referent		Referent	
II	12.31 (4.13 to 36.71)	<.001	1.08 (0.81 to 1.43)	.60
III	66.30 (19.78 to 222.24)	<.001	1.46 (0.91 to 2.35)	.12
IVA	72.39 (18.91 to 277.08)	<.001	2.28 (1.28 to 4.08)	.005
IVB	121.72 (33.63 to 440.61)	<.001	1.83 (1.09 to 3.07)	.02
Surgery		.01		<.001
Yes	Referent		Referent	
No/Unknown	3.80 (1.38 to 10.43)	.01	3.71 (1.79 to 7.69)	<.001
Adjuvant radiotherapy		.003		<.001
Yes	Referent		Referent	
No/Unknown	1.68 (1.20 to 2.35)	.003	1.71 (1.42 to 2.04)	<.001
Adjuvant chemotherapy		<.001		.59
Yes	Referent		Referent	
No/Unknown	0.26 (0.14 to 0.50)	<.001	0.78 (0.31 to 1.94)	.59
LNR				.03
I	—		Referent	
II	—		1.40 (1.09 to 1.81)	.01
III	—		1.26 (0.96 to 1.64)	.09
LODDS		<.001		
I	Referent		—	

(continued)

Table 4. (continued)

Variables	Cause-specific death		Death due to other causes	
	HR (95% CI)	P[a]	HR (95% CI)	P[a]
II	2.98 (1.73 to 5.14)	<.001	—	
III	3.64 (2.19 to 6.02)	<.001	—	

[a]The *P* values were calculated by Fine and Gray subdistribution hazards model and were 2-sided. AJCC = American Joint Committee on Cancer; CI = confidence interval; HR = hazard ratio; LNR = lymph nodes ratio; LODDS = log odds of positive lymph nodes; NOS = not otherwise specified; — = not available.

[HR] = 4.36, 95% confidence interval [CI] = 2.12 to 8.96; $P < .001$), pathological grade IV (vs grade I: HR = 5.87, 95% CI = 2.67 to 12.88; $P < .001$), tumor size of at least 4 cm (vs tumor size <2 cm: HR = 1.89, 95% CI = 1.18 to 3.03; $P = .008$), papillary microcarcinoma (vs papillary adenocarcinoma: HR = 0.00, 95% CI = 0.00 to 0.00; $P < .001$), AJCC-8 stage ($P < .001$), surgery status ($P = .01$), adjuvant radiotherapy status ($P = .003$), adjuvant chemotherapy status ($P < .001$), LODDS II (vs LODDS I: HR = 2.98, 95% CI = 1.73 to 5.14; $P < .001$), and LODDS III (vs LODDS I: HR = 3.64, 95% CI = 2.19 to 6.02; $P < .001$).

Similarly, the competing risks model for DOC indicated that the age 55 years or older (vs age younger than 55 years: HR = 5.24, 95% CI = 3.99 to 6.87; $P < .001$), year of diagnosis of 2010-2012 (vs 2013-2015: HR = 1.27, 95% CI = 1.05 to 1.54; $P = .01$), female (vs male: HR = 0.50, 95% CI = 0.42 to 0.60; $P < .001$), pathological grade III (vs grade I: HR = 1.83, 95% CI = 1.08 to 3.12; $P = .03$), pathological grade IV (vs grade I: HR = 2.19, 95% CI = 1.05 to 4.56; $P = .04$), tumor size of at least 4 cm (vs tumor size <2 cm: HR = 1.50, 95% CI = 0.93 to 1.41; $P = .002$), AJCC-8 stage IVA (vs AJCC-8 stage I: HR = 2.28, 95% CI = 1.28 to 4.08; $P = .005$), AJCC-8 stage IVB (vs AJCC-8 stage I: HR = 1.83, 95% CI = 1.09 to 3.07; $P = .02$), surgery status ($P < .001$), adjuvant radiotherapy status ($P < .001$), and LNR II (vs LNR I: HR = 1.40, 95% CI = 1.09 to 1.81; $P = .01$) were statistically significant prognostic risk factors. Table 4 presents the variables identified in the multivariate analysis of the competing risks model.

Nomogram Construction and Verification

Based on the variables derived from the competing risks model, we established nomograms for CSD and DOC (Figure 3). The prognostic factor with the greatest influence was the histological type for the CSD nomogram and the pathological grade for the DOC nomogram. After successfully constructing the nomograms, we used the validation cohort to verify them.

For the CSD nomogram, the 1-year, 3-year, and 5-year C-indexes were 0.958, 0.942, and 0.907, respectively, for the training cohort, and 0.942, 0.931, and 0.913 for the validation cohort. For the DOC nomogram, the 1-year, 3-year, and 5-year C-indexes were 0.798, 0.795, and 0.772, respectively, for the training cohort, and 0.813, 0.746, and 0.776 for the validation cohort. In addition, as shown in Figure 4, calibration plots showed good consistency in both nomograms, because the predicted values (solid lines) used in the training and validation cohorts were very close to the actual values (dotted lines).

Discussion

This study used the latest edition of the AJCC staging system, which is a huge improvement over previous editions because major adjustments have been made to thyroid cancer (27). The increase in the age threshold for thyroid cancer from 45 to 55 years in the eighth edition will be clinically relevant to thousands of patients worldwide. After raising the age cutoff, the AJCC stage of some elderly patients has been reduced, and the survival time of these elderly patients is indeed more in line with the low-level stage, which indicates that they are currently incorrectly assigned to the higher-level stage category (23). We have used the latest staging system to construct novel prognostic nomograms for DTC, which will effectively improve the correct grouping of patients between the ages of 45 and 54 years, thereby more accurately predicting the prognosis of patients.

Among the demographic indicators, age and sex have previously been found to be important prognostic indicators for DTC patients (28,29). We similar found that those aged older than 55 years and sex are related to DOC; however, these variables were not found to be related to CSD. The possible reason is that an individual's life expectancy is highly dependent on age and sex. Age is closely related to aging or death. As the age increases, the death rate of an individual also increases (30). Studies have shown that over the last few decades, the life expectancy of women systematically exceeds that of men (31). Therefore, these prognostic factors related to DOC are not the best direction to reduce the specific mortality of DTC patients. On the contrary, these factors require the common attention of the whole society. Similarly, the year of diagnosis is a highly statistically significant predictor of DOC but not CSD. This is most likely because of improvements in medical technology that have improved the overall survival rate of patients.

Among the clinicopathological indicators, we found that pathological grade, tumor size, AJCC-8 stage, surgery status, and adjuvant radiotherapy status are related to both CSD and DOC, whereas histological type and adjuvant chemotherapy status are DTC-specific prognostic factors. Akslen and LiVolsi (32) found that tumor size and pathological grade showed statistically significant and independent prognostic importance for papillary thyroid carcinoma. The influence of the histological type of DTC on the prognosis remains controversial in the literature. Another study found that the papillary and follicular histological types can improve survival predictions of the prognostic model (33). Our study further subdivided histological types and found that different histological types did produce different DTC-specific survival rates in the multivariate CSD analysis. However, this difference needs to be further investigated in future studies.

The AJCC staging system has always been important in the prognosis of DTC. Some previous studies have performed analyses based on AJCC-8 stage, with their results showing that this edition is more accurate for discriminating mortality and prognosis in DTC patients (34,35). The present study also found that AJCC-8 stage is an important indicator of the prognosis of DTC patients, in terms of both CSD and DOC.

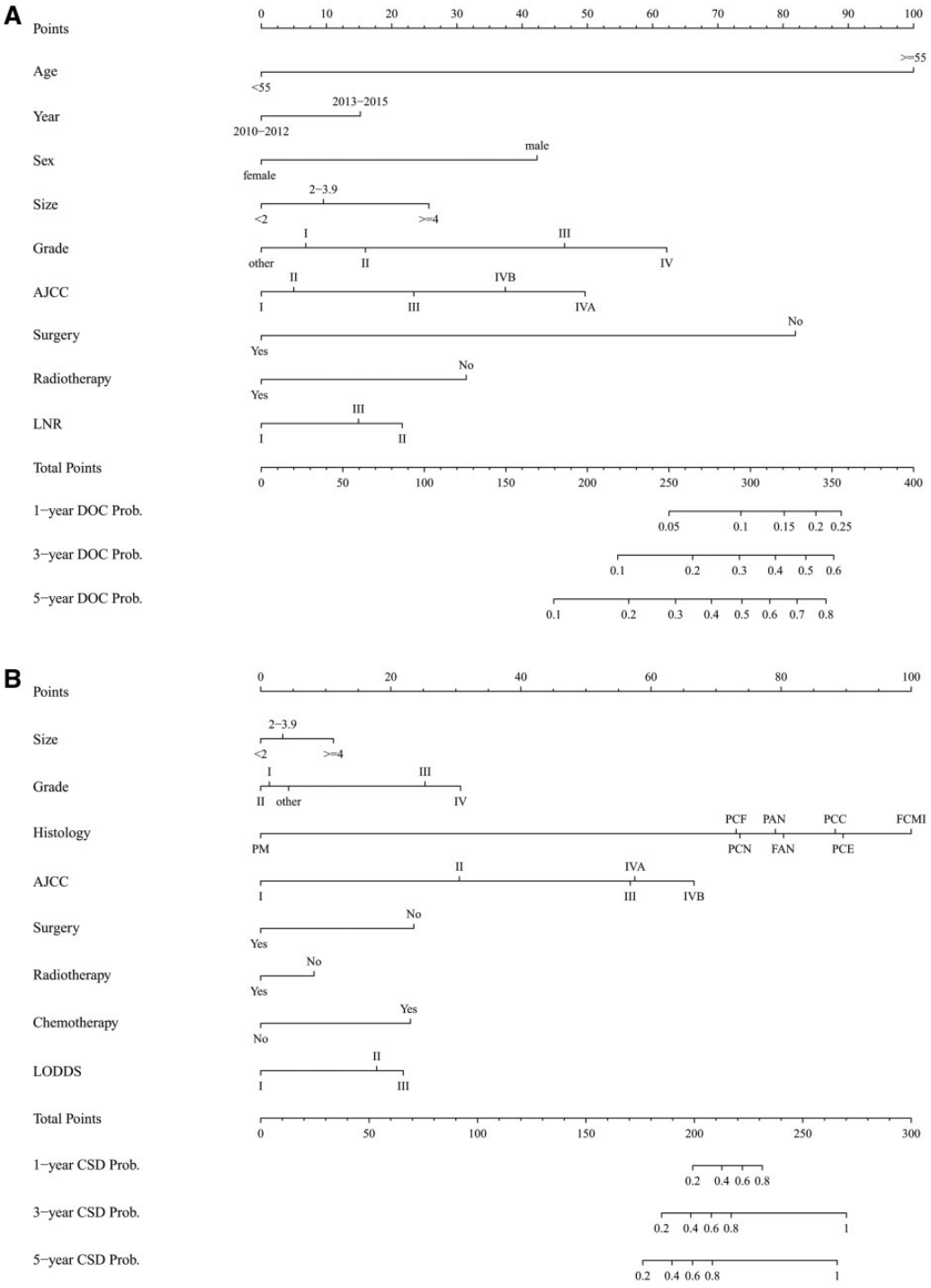

Figure 3. Nomograms. Nomograms based on the competing risks analysis to predict cancer-specific death probabilities **(A)** and death due to other causes probabilities **(B)** at 1 year, 3 years, and 5 years. AJCC = American Joint Committee on Cancer; FAN = follicular adenocarcinoma; FCMI = follicular carcinoma, minimally invasive; LNR = lymph node ratio; LODDS = log odds of positive lymph nodes; PAN = papillary adenocarcinoma; PCC = papillary carcinoma, columnar cell; PCE = papillary carcinoma, encapsulated; PCF = papillary carcinoma, follicular variant; PCN = papillary carcinoma; PM = papillary microcarcinoma.

It has recently been reported that surgery and radioiodine therapy followed by levothyroxine substitution are the established therapeutic procedures for DTC (36). Our study analogously found that surgery and radiotherapy are prognostic factors for DTC. In particular, chemotherapy was also a prognostic factor for DTC but not for DOC, which suggests that chemotherapy does not improve the overall survival rate of patients but deserves more in-depth research as a prognostic factor of CSD. Regrettably, the information in the SEER database regarding specific treatments is inadequate, and so we consider that more detailed data need to be obtained in the future.

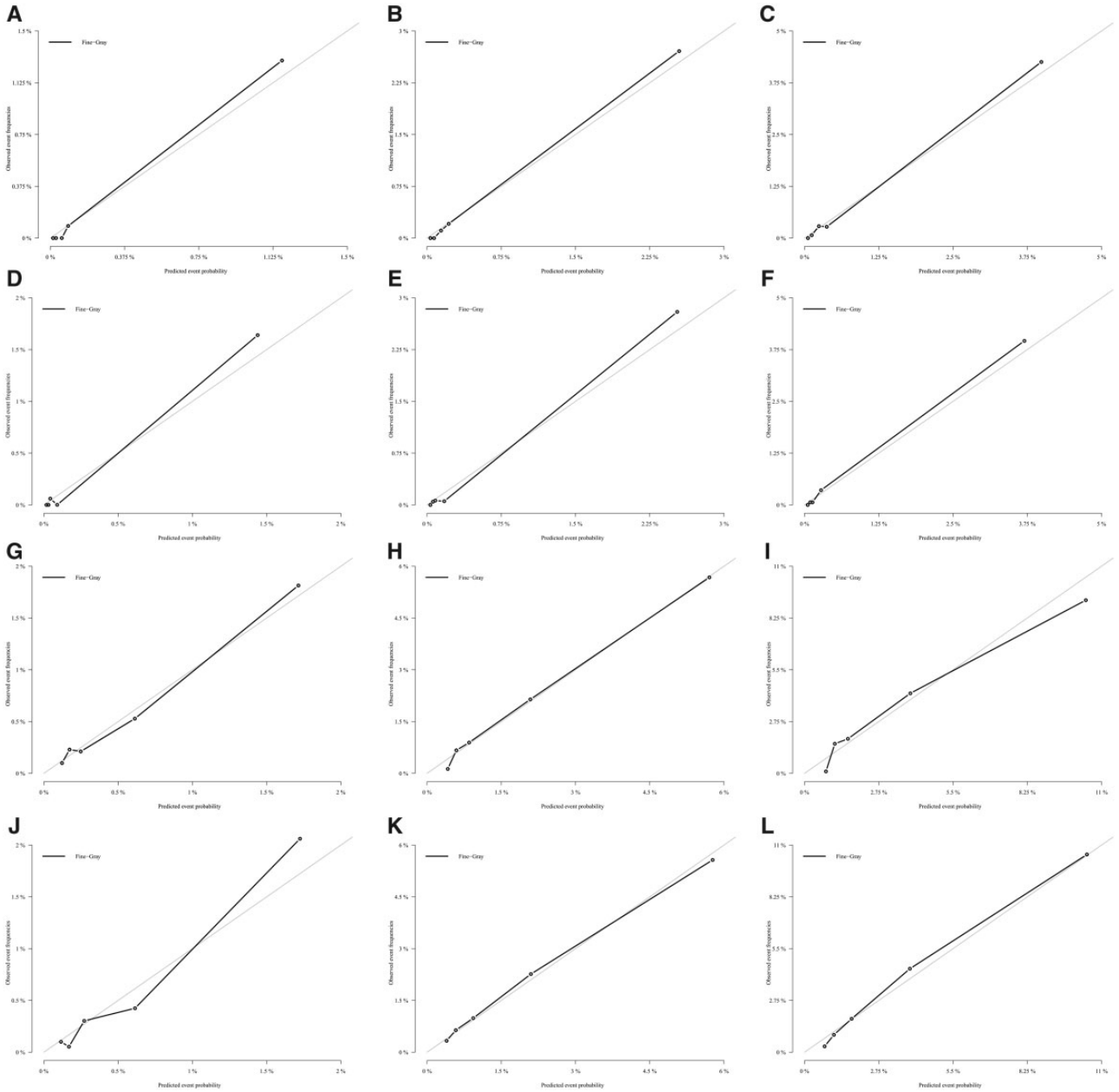

Figure 4. Calibration curves. Calibration curves of 1-year, 3-year, and 5-year calibration plots of the training **(A, B, C)** and validation **(D, E, F)** cohort for cancer-specific death. Calibration curves of 1-year, 3-year, and 5-year calibration plots of the training **(G, H, I)** and validation **(J, K, L)** cohort for death due to other causes.

Our study compared the prognostic ability of different lymph node indicators in CSD and DOC models. It is noteworthy that our DTC nomograms are the first to include LNR and LODDS. Recent studies have found these 2 indicators to be related to the prognosis of various cancers, with their prognostic performance being better than those of traditional lymph node indicators (37–39). However, we are not aware of any similar previous studies of DTC patients. Our study included LODDS in the CSD nomogram and LNR in the DOC nomogram. The goodness of fit of the LODDS in the CSD model and the LNR in the DOC model is higher than other lymph node indicators, which suggests that these emerging indicators have good prognostic functions.

Nomograms have been widely used as a tool for predicting the survival time of individual patients. Our study used a competing risks model to analyze the prognostic factors for the CSD and DOC outcomes of DTC patients more accurately. Our results show that among all the patients who died, 77.5% of the patients died because of competitive events. If the traditional Cox proportional hazards model was used, the cumulative incidence rate would be overestimated (40). The Fine and Gray regression model can solve this problem well. It focuses on the cumulative risk of a specific outcome and is more suitable for constructing a predictive model for diseases with a good prognosis and a high proportion of the elderly population (41). In general, our model is based on AJCC-8 stage and is more comprehensive. It can be used as a tool to help clinicians individually predict the probability of CSD and DOC in DTC patients at 1

year, 3 years, and 5 years, which has certain guidance in clinical applications.

Inevitably, this study had some limitations. First, the SEER database has some inherent limitations, such as imprecise information about treatment methods. Although this study has added some new variables, it lacked some DTC prognostic factors such as the *BRAF* proto-oncogene. Second, the data in this study are representative of the US population, and because the onset and prognostic characteristics of DTC may differ among populations in different regions, further research is needed to determine the applicability of the results outside the United States. Third, retrospective data may bring bias to our study, and it is worth noting that because the year of diagnosis was 2010-2015 and the cutoff time for database records was the end of 2016, the data of 2014-2015 diagnostic year failed to monitor the 3-year and 5-year incidence rate, and the data of 2012-2013 diagnostic years failed to monitor the 5-year incidence rate. The existence of these censored data may make these data not fully utilized and bias the results, and so the findings will need to be verified in a more complete prospective cohort study.

We have constructed and verified 1-year, 3-year, and 5-year prognostic nomograms for DTC patients based on the competing risks model, which yielded very good results. Our model is based on demographic and clinical big data and includes the AJCC-8 stage in the prognosis. Moreover, this is the first time that LNR and LODDS indicators have been included in prognostic nomograms.

All of these characteristics reflect considerable advantages of the present model. We believe that the findings of this study can guide clinicians and researchers to make more convenient and more scientific judgments on the prognostic factors of DTC patients. Prospective data on other demographic characteristics should be used to verify our results by some cross-validation approach in the future.

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Notes

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Data Availability

The data sets generated and/or analyzed during the current study are available in the SEER database (https://seer.cancer.gov/).

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